REMARKS/ARGUMENTS

In response to the Office Action mailed January 7, 2009, Applicant amends his application and requests reconsideration. Claims 1-25 were originally pending in this application. Claims 1-10 and 18-25 are cancelled, however Applicant reserves the right to present the claimed subject matter in a divisional application. Claims 11-17 are pending and undergoing examination.

Claims 11 and 13-15 have been amended to further clarify and refine that which Applicant considers to be the invention. While the specification as filed makes it clear that the claimed invention can be used for transplantation, the claims as now amended include the feature that the inventions claimed are suitable for transplantation onto a damaged cornea. In addition, the claims were amended to change the word "in" to "within" to further clarify that the growth factors are incorporated within the biopolymer. These amendments are fully supported in the specification as filed, including [0032]-[0035], and at least, in Examples 11-18. No new matter has been added by these amendments.

Discussion of the Claim Objections

The Examiner objected to claims 13-15 because the Examiner asserts that the abbreviation "HCEC" in the claims is ambiguous even though the term is explicitly defined in the specification. In the interest of advancing prosecution, Applicant has amended claims 13-15 by deletion of the term "HCEC" and substitution of the phrase "human corneal endothelial cells" as defined in Applicant's specification. Applicant requests withdrawal of this objection.

The Examiner objected to claim 7 as depending from a non-elected claim. It is assumed by Applicant that the Examiner meant to object to claim 17 as depending from claim 1, because claim 7 was withdrawn. Applicant has amended claim 17 to depend from claim 11, and requests withdrawal of the objection as moot.

Discussion of the Rejections under §112, second paragraph

The Examiner maintained the rejections of claims 11-17 under 35 U.S.C. §112, second paragraph, for failing to point out and distinctly claim Applicant's invention. The Examiner alleges that the cell culture attachment reagent known as RGDS, a tetrapeptide consisting of Arginine-Glycine-Aspartic acid-Serine, could be confused by those of ordinary skill in the art with another abbreviation or acronym having the same four letters, and therefore must be further identified. The Examiner states that because it is a peptide of four amino acids in length, the sequence rules require that it must have a sequence listing, even though this reagent has been present in other issued patents without having a sequence listing. In order to further prosecution, Applicant submits with this reply, a new Sequence Listing and statement under 37 C.F.R. §1.821, identifying the tetrapeptide named RGDS as SEQ ID NO: 1. In addition, Applicant has amended the claims to recite the SEQ ID NO when RGDS is referred to in the claims. In view of the foregoing, Applicant requests withdrawal of this rejection.

Discussion of the Novelty Rejection

The Examiner maintained the rejection claims 11-13 and 17 under 35 U.S.C. §102(b), as anticipated by USP 5,827,641 to Parenteau et al. According to the Examiner, Parenteau et al. allegedly teach an artificial corneal transplant support and transplant, comprising a biopolymer with attachment factors, is in the shape of a cornea, and has an inner endothelial layer. Applicant respectfully traverses this rejection.

First, Applicant respectfully points out that Parenteau et al. teaches an *in-vitro* corneal model, and does not teach a corneal transplant. Second, there is no teaching anywhere in Parenteau et al., that the corneal biopolymer support taught in Parenteau et al. contains within it, any growth factors such as laminin, fibronectin, RGDS (SEQ ID NO: 1), bFGF conjugated with polycarbophil, EGF conjugated with polycarbophil as claimed by Applicant. There is also no teaching or suggestion that the support taught in Parenteau et al. is suitable for transplantation into a damaged cornea. The Examiner alleges that Parenteau et al. teach the use of heparin and heparin binding

growth factor. However, those heparin compounds are not incorporated *within* the biopolymer. The heparin and heparin binding growth factor referred to are components of the MSBM cell culture media discussed in col. 6 of Parenteau et al. There is no teaching of any growth or attachment factors being incorporated within the biopolymer support as claimed by Applicant. Finally, Parenteau et al. does not teach that the support is made in the shape of a cornea, merely that it is grown in a cell culture dish.

Parenteau et al. do not teach each and every element of Applicant's amended claims, and therefore they cannot be anticipated under 35 U.S.C. §102(b). As such, Applicant respectfully requests withdrawal of the rejection.

Discussion of the Obviousness Rejection

The Examiner also maintained the rejection of claims 11-17 under 35 U.S.C. §103(a), as unpatentable, over Parenteau et al., in view of USP 6,645,715 to Griffith et al., and USP 6,689,165 to Jacob et al. According to the Examiner, Parenteau et al. fail to teach a half-thickness corneal support as recited in claims 14-16, and also fails to teach any of the attachment factors claimed by Applicant. Griffith et al. is offered by the Examiner for teaching the attachment factors such as laminin, fibronectin, bFGF and the like. The Examiner offers Jacob et al. for teaching that epithelial cell adhesion is augmented by growth factors on the polymer surface of an artificial corneal construct. The Examiner then concludes that it would have been obvious to one of ordinary skill in the art, at the time the invention was made, to modify the construct of Parenteau et al., with the attachment factors of Griffith et al. Applicant traverses this rejection.

For subject matter defined by a claim to be considered obvious, the Office must demonstrate that the differences between the claimed subject matter and the prior art "are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains." 35 U.S.C. § 103(a); see also *Graham v. John Deere Co.*, 383 US 1, 148 USPQ 459 (1966). The ultimate determination of whether an invention is or is not obvious is based on certain factual inquiries including: (1) the scope and

content of the prior art; (2) the level of ordinary skill in the prior art; (3) the differences between the claimed invention and the prior art, and (4), objective evidence of nonobviousness. *Graham*, 3838 US at 17-18, 148 USPQ at 467.

Consideration of the aforementioned Graham factors here indicates that the present invention, as defined by the amended claims, is unobvious in view of specification and claims of the present patent application.

With regard to the differences between the cited references and Applicant's invention, Applicant submits that none of these references teaches a biopolymer having growth and attachment factors incorporated *within* the biopolymer that is suitable for transplantation into a damaged cornea, as now claimed by Applicant. Parenteau et al. was discussed above. As stated previously, Griffith et al. teach an *in-vitro*, avascular, human corneal equivalent, comprising immortalized human cell lines, not a corneal biopolymer support suitable for transplant into a cornea (abstract, col.7 – col. 8). All the teachings or examples in Griffith et al., where a biopolymer support suitable for long term growth of HCEC is produced, use only immortalized cells which cannot be transplanted. The growth factors mentioned in Griffith et al. are in the media, and used to test the cell lines, not incorporated in the biopolymer support as claimed by Applicants (Griffith at col. 7). Moreover, because the construct of Griffith et al. is for *in-vitro* testing, there is no teaching of shaping the biopolymer for use in a cornea.

Jacob et al. teach an ocular device comprising an optical polymer having biocompatible linear, single chain tether molecules having two ends, attached to the optical polymer on one end of the tether, and a corneal enhancer molecule or growth factor attached to the tether at the other end. As Applicant discussed previously, the device of Jacob et al. is designed for growth of corneal epithelial cells on the convex or outside surface of the device. In contrast, Applicant's invention is directed to an artificial stroma for growth of corneal endothelial cells on the concave or inside surface of the cornea. The cell type taught in Jacob et al. is completely different than the cell type used by Applicant. Jacob et al. also teach that the corneal enhancer molecules or growth factors must be tethered to the optical polymer via a linear polyethylene oxide (PEO) molecule, or amino acid or peptide, with a molecular

weight between 2000-8000. Applicant's claimed support does not use any such chemical modifications.

For purposes of the present analysis, Applicants consider that the level of ordinary skill in the art can be considered to be reasonably high, such that a person of ordinary skill in the relevant art would have an advanced degree in chemistry and/or chemical engineering, as well as several years of experience in the relevant field of ophthalmology.

Considering all of the Graham factors together, it is clear that the Applicant's invention, as presently claimed, would not have been obvious to one of ordinary skill in the art, at the relevant time, in view of the prior art references. Furthermore, a rationale to support a conclusion that a claim would have been obvious requires that all the claimed elements were known in the prior art and one skilled in the art could have combined the elements as claimed by known methods with no change in their respective functions, and the combination would have yielded nothing more than predictable results to one of ordinary skill in the art. *KSR International Co. v. Teleflex Inc.*, 550 US 398, 408, 82 USPQ2d 1385, 1395 (2007).

The Court in *KSR* noted that obviousness cannot be proven merely by showing the elements of a claimed device were known in the art; it must be shown that those of ordinary skill in the art would have had some "apparent reason" to combine the known elements in the fashion claimed. *KSR* at 1741. In the same way, when the prior art teaches away from the claimed invention, as shown in Appellant's arguments and other objective evidence, obviousness cannot be proven by merely showing that the biopolymer composition and growth factors were known, and corneal endothelial cells could be modified by routine experimentation. See, *Ex parte Whalen* II, Appeal 2007-4423, (BPAI July 23, 2008) at pp. 13-16.

Applicant submits that one of ordinary skill in the art, in an attempt to improve corneal endothelial grafts, when reading Parenteau et al., in view of Griffith et al. and Jacob et al., would not have expected that Applicant's invention would work, because Parenteau et al. and Griffith et al. do not teach anything about implantable corneal constructs. Further, Griffith et al. teach that only transformed endothelial cells are able to maintain sustained growth in culture. Jacob et al. teach that the growth factors

must be covalently bound to the optical polymer (not incorporated within it) to allow cell growth, and teaches the use of epithelial cells on outer or convex surface of the cornea, not the use of endothelial cells on the inner, or concave surface as Applicant claims. In Applicant's invention, the combination of attachment factors do not have to be covalently bound, but only mixed into the polymer, to be effective. Applicant's claimed method is simpler, and more effective and less costly, as there are no synthesis steps for making the tethered growth factors. Moreover, Applicant's cornea will not be susceptable to eventual swelling and loss of clarity.

Furthermore Applicant submits that the combination of Parenteau et al., in view of Griffith et al. and Jacob et al. does not make Applicant's claimed invention *prima facie* obvious, because: 1) the combination of references does not teach each and every element of Applicant's claimed invention, namely, the combination of references does not teach both the use of non-transformed human corneal endothelial cells, and the use of a biopolymer having growth factors incorporated into it and shaped as a cornea, which is suitable for transplantation; and 2) the combination of references teaches away from Applicant's invention because the primary reference of Parenteau et al. and Griffith et al. are directed to immortalized human corneal endothelial cells (not cells from a patient's cornea), which could never be ethically implanted into a patient for fear of cancer, and Jacob et al. is directed to a completely differnent corneal cell type.

The Examiner's reliance on *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981) is misplaced. Applicant has not attacked the references individually. Applicant has discussed the teachings of each cited reference, and then has shown that when the *combination of references* is considered, the *combination* of teachings cannot render Applicant's claimed invention, *as a whole*, *prima facie* obvious, because the combination of teachings do not encompass all of Applicant's claimed features, and because the combination of teachings teach away from Applicant's claimed invention. As such, Applicant respectfully requests withdrawal of this rejection.

Conclusion

Applicant respectfully submits that the patent application is in condition for allowance. If, in the opinion of the Examiner, a telephone conference would expedite

the prosecution of the subject application, the Examiner is invited to call the undersigned attorney.

Respectfully submitted,

Joseph G. Contrera, Reg. No. 44,628
LEYDIG, VOIT & MAYER
700 Thirteenth Street, N.W., Suite 300
Washington, DC 20005-3960
(202) 737-6770 (telephone)
(202) 737-6776 (facsimile)

Date: April 6, 2009

JAW/JGC/jj

H:\Joe\Cellular Bioengineering\404339 Second OA Response.doc